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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: T. Kosoglou et al.	:	Examiner: San-Ming R. Hui
Serial No.: 10/056,680	:	Group Art Unit: 1617
Filed: January 25, 2002	:	Atty. Docket No.: CV01492K
For: Combinations of Sterol Absorption Inhibitor(s) with Blood Modifiers for Treating Vascular Indications	:	

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HARRY DAVIS, Jr., Ph.D.

I, Harry Davis, Jr., declare and state that:

1. I obtained a Bachelor of Science in Animal and Veterinary Science degree from the University of Maine in 1977.

2. I obtained a Master of Science in Anatomical Pathology degree from George Washington University in 1979.

3. I obtained a Doctorate Degree in Pathology from the University of Chicago in 1982.

4. I am employed by Schering-Plough Research Institute ("Schering") as a Distinguished Research Fellow in the field of Cardiovascular and Metabolic Disease and have

been employed in this capacity since 1993 and was previously employed by Schering as a Principal Scientist since November 1987.

5. My duties at Schering have included pharmaceutical drug discovery and basic research in lipid absorption and metabolism and metabolic disease.

6. Hypercholesterolemia has been associated with an increased sensitivity for platelets to aggregate and cause vascular complications. A study was conducted under my supervision to determine if a reduction in plasma cholesterol levels by ezetimibe (EZ) would enhance the ability of aspirin (ASA) to act as a platelet aggregation inhibitor. Rats were fed a 1% cholesterol + 0.5% cholate diet (HC) alone or containing ezetimibe (0.0036%, 3 mg/kg/day) for 7 days. On day 7 they were treated with aspirin at 100 mg/kg or vehicle, and platelet aggregation determined. Mean plasma cholesterol levels were reduced from 344 ± 22 mg/dl to 60 ± 4 mg/dl by ezetimibe treatment. Platelet aggregation by adenosine diphosphate (ADP) and collagen was not altered, as expected, among the groups. Arachidonic acid (AA) induced platelet aggregation at 0.3 mM was increased by the hypercholesterolemic diet compared to normal chow fed rats (Table), indicating an increased sensitivity to aggregate with hypercholesterolemia. AA induced aggregation was not reduced in the aspirin alone treated hypercholesterolemic animals. AA induced aggregation was significantly reduced in the aspirin + ezetimibe treated rats compared to the aspirin alone treated hypercholesterolemic rats (Table).

Table: Platelet Aggregation

Agonist	Regular Chow	High Cholesterol (HC) diet	HC + EZ	HC + ASA (100 mpk)	HC + EZ + ASA (100 mpk)
AA (0.3 mM)	7 ± 3	14 ± 2	13 ± 2	12 ± 2	7 ± 2
AA (1 mM)	16 ± 2	17 ± 3	16 ± 3	14 ± 2	5 ± 2
ADP (10 μM)	24 ±1	21 ± 2	21 ± 3	25 ± 2	31 ± 1
Collagen (3 μg/ml)	25 ± 1	24 ± 3	27 ± 3	30 ± 2	32 ± 1

Aggregation in whole blood (ohms)

N=6 per group, Mean ± SEM

In my opinion, these results indicate that the combination of ezetimibe with aspirin synergistically and unexpectedly enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Jan 3, 2007

HARRY DAVIS, Jr., Ph.D.